

REMARKS

Claims 1-7, 14, and 29-39 are pending. Claims 31-33 are allowed. Claims 1-7, 14 and 29-30 are rejected. Claims 1 and 3-7 are amended herein. Support for the amendment to Claim 1 is found, for example, at page 23, lines 8-9; page 72, lines 7-28; and page 79, Table 1. Support for the amendments to Claims 3-7 is found, for example, at page 9, line 18 to page 10, line 17; page 11, line 23 to page 20, line 21; page 22, line 27 to page 25, line 21; and page 70, line 25 to page 74, line 15. New Claims 34-39 are added. Support for these claims is found, for example, at page 70, line 25 to page 74, line 15 and page 79, Table 1.

No new matter is introduced by way of this Amendment. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Formalities

The Examiner objects to be specification under 37 C.F.R. § 1.821(d) for failing to provide sequence identifiers for the ten sequences on page 29, lines 1-7.

On November 4, 2002, Applicants filed "Response to Notice to Comply with Sequence Rules and Amendment re Sequence Listing." In the Response, Applicants submitted: (i) an amendment in which sequence identifiers were provided for the ten amino acid sequences on page 29, lines 1-7; (ii) a paper copy of the substitute Sequence Listing; (iii) a computer readable form of a substitute Sequence Listing; and (iv) a statement that the computer readable form is identical the paper copy. Therefore,

Applicants submit that the Response filed November 4, 2002 brings the application into condition of adherence to 37 C.F.R. § 1.821-1.825.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-7, 14, and 29-30 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

a. Claims 1-7 and 14 stand rejected as being indefinite in the recitation of “integrin I domain.” The Examiner contends it is unclear if the integrin I domain is αM , αL , $\alpha 2$ or $\alpha 1$.

M.P.E.P. § 2111.01 sets forth the mode for interpreting claim language during examination:

During examination, the claims must be interpreted as broadly as their terms reasonably allow. This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). . . .

The specification beginning at page 22, line 28, sets forth Applicant’s definition of “integrin I domain.” This definition includes a discussion of the term and provides examples, synonyms, and a publication that is incorporated by reference. Therefore, the definition provided in the specification is clear and M.P.E.P. § 2111.01 requires that this definition be used to interpret “integrin I domain” as recited in the claims. Interpreting the term in view of the specification, Applicants submit that “integrin I domain” includes but is not limited to the examples of integrin I domain proteins cited by the Examiner.

Applicants respectfully assert that “integrin I domain” is not indefinite and respectfully request that the rejection of Claims 1-7 and 14 under 35 U.S.C. § 112, second paragraph be withdrawn.

b. Claims 1, 29, and 30 stand rejected as being indefinite in the recitation of “about 98% identical to human integrin I domain” or “98% identical to the wild-type protein” because sequence identifiers are not provided.

In responding to the rejection, Applicants have interpreted the Examiner’s comments to mean that the recitation of percent homology without providing a sequence identifier for the reference protein and not the claimed protein renders the claim indefinite and ambiguous because different laboratories may have the same name for a different protein. Thus, Applicants assume that Claims 1, 29, and 30 stand rejected because “human integrin I domain protein” and “wild-type protein” do not have sequence identifiers.

As stated above, the mode for interpreting claim language during examination requires that “the words of a claim be given their plain meaning unless applicant has provided a clear definition in the specification.” M.P.E.P. § 2111.01.

Applying this requirement to “integrin I domain protein,” Applicants submit that the response to the rejection of Claims 1-7 and 14 above is relevant to the response to the present rejection of Claim 1 to the extent that the rejection is based on the meaning of this term. As previously stated, “integrin I domain” is not indefinite because the term is clearly defined in the specification. In addition, the term “human” further limits the term to integrin I domain proteins of human beings.

Regarding the term “wild-type,” Applicants submit that M.P.E.P. § 2111.01 requires that this term be given its plain meaning. To this end, Applicants quote the definition of the term set forth in the *Oxford English Dictionary*:

wild type. *Genetics.* The type of strain, gene, or characteristic that prevails among individuals in natural conditions, as opposed to an atypical mutant type.

(2nd ed. 1989). The definition is followed by a number of examples, which include:

1946 *Nature* 19 Oct. 558/1 These include wild type strains [of *E. coli*] with no growth-factor deficiencies, and single mutant types requiring only thiamin or phenylalanine. 1970 *Sci. Amer.* Mar 103/1 Most mutant genes are nonfunctional or do something very different from wild-type genes, so that they can be easily distinguished.

Id.

In view of the plain meaning of “wild-type,” Applicants submit that Claims 29 and 30 are drawn to an integrin that is crystallized with its ligand. The integrin comprises noncontiguous alterations that bias the integrin into either an open or closed conformation and has an amino acid sequence that is less than 98% identical to its unaltered, wild-type counterpart.

In view of the above, Applicants respectfully assert that Claim 1, 29, and 39 are not indefinite and respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

c. Claims 3-7 are indefinite in the recitation of positions of amino acid substitutions without providing sequence identifiers.

Claims 3-7 are amended herein to recite “positions of the human alpha-M I domain protein.” The amino acid positions recited in the claims are set forth

in the specification beginning on page 71, line 32. Thus, each position is clearly defined in the specification.

Applicants respectfully assert that Claims 3-7 are not indefinite and respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

d. Claim 3 stands rejected as indefinite for being in improper Markush format.

Claim 3 is amended herein by the insertion of the phrase “selected from the group consisting of” and the conjunction “and” in the list of positions. The insertion of these terms necessitated further amendments to Claim 3 for clarity.

In view of these amendments, Applicants respectfully assert that Claim 3 is not indefinite and respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

e. Claims 4-7 stand rejected as indefinite for being in improper format.

The amendments herein to Claims 4-7 are necessitated by the amendments to Claim 3, from which Claims 4-7 depend. Thus, Applicants submit that these amendments are to maintain proper antecedent basis with Claim 3.

In view of the amendments to Claims 3 and 4-7, Applicants respectfully assert that Claims 4-7 are not indefinite and respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

f. Claim 1 stands rejected for reciting “less than about.” The Examiner contends a skilled artisan would not know if the claim means 1%, 50%, or even more.

Claim 1 is amended herein by the deletion of the term “about.”

Applicants respectfully assert that Claim 1 is not indefinite and respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

a. Claims 1-7, 14, and 29-30 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

It is well settled law that the specification is not required to teach every detail of the invention. Rather, the specification need only explain how to make and use the invention without requiring an inordinate amount of experimentation. The test of enablement is not whether experimentation is necessary, but if experimentation is necessary, whether it is undue. See *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The determination of whether an invention requires undue experimentation is based on a number of factors, including:

1. the quantity of experimentation necessary;
2. the amount of direction or guidance presented in the application;
3. the presence or absence of working examples;
4. the nature of the invention;
5. the state of the prior art;
6. the relative skill of those in the art;
7. the predictability or unpredictability in the art; and,
8. the breadth of the claimed invention.

See *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). It is not necessary that every analysis consider all eight factors when determining if experimentation is undue.

Of the above factors, the Examiner's rejection appears to be primarily concerned with factor 7, the unpredictability of the computational method.

Applicants note that U.S. Patent No. 6,188,965 (attached as Exhibit A), provides a detailed description and actual experimental exemplification of how to make and test a number of diverse protein variants (GCN4, λ repressor, ZIF268, and G β 1) designed by the computational method of the present invention. Applicants further note that U.S. Patent No. 6,403,312 (attached as Exhibit B), provides a detailed description of the computational method used in the invention to pre-screen libraries of beta-lactamase and xylanase. Therefore, these exhibits further illustrate the predictability of the computational method used in the present invention and its ability to allow the routine automated protein design of a large number of proteins, which can be tested for any property.

Moreover, Applicants submit that the amount of direction or guidance presented in the application is sufficient to allow someone of skill in the art to make and use the claimed invention. The PDA™ method, its application to the integrin I domain proteins to generate variants, and methods of making and testing have been well described in the specification. See pages 11-20 for a description of the PDA™ method and pages 70-74 describe ways of making the integrin I domain proteins of the invention. Thus, the specification is sufficiently enabled to allow one of skill in the art to make and use the variant integrin I domain proteins of the present invention.

Finally, Applicants submit that Burgess, *et al.* (1990) *J. Cell Biology* 111:2129-2138 and Lazar, *et al.* (1988) *Mol. Cell. Biol.* 8:1247-1252 are not proper references to demonstrate the unpredictability of the present invention. Burgess, *et al.* describe a mutant HBGF-1 in which a random substitution of a glutamic acid residue for a lysine reduced the affinity of HBGF-1 for immobilized heparin but did not reduce the affinity of HBGF-1 for the HBGF receptor. Similarly, Lazar, *et al.* describe the random mutagenesis of conserved, charged amino acid positions in TGF- α that may result in either no change or a decrease in biological activity. Thus, the approach used by Burgess, *et al.* and Lazar, *et al.* is to randomly alter charged amino acid positions and to screen for a protein with an altered biological activity. That is, the goal is to produce mutants that exhibit a loss of function to facilitate the identification of amino acids required for biological activity which is equated to binding to another molecule.

In contrast, the PDATM method begins by classifying each amino acid position as a surface, boundary or core residue, and the residue positions are classified as either fixed or variable. For each variable position, a set of amino acid side chain rotamers are chosen, with at least one variable residue position having rotamers from at least two different amino acid side chains. The calculation then proceeds as follows: for each variable position, the energy of interaction of each rotamer with both the template (*e.g.* anything that is fixed, including the backbone and any fixed residues) and all possible rotamers at all variable positions is calculated. This is done using any number of different scoring functions. That is, the scoring functions are each components that can be used to calculate the energy of interaction: based on hydrophobicity, solvation, hydrogen bonding, electrostatics, etc. By screening all possible sequences for each

position that can be occupied, a set of optimal sequences for the protein backbone is identified. Thus, the goal of the PDA™ method is to produce variants in which at least one physical, chemical or biological property of the variant is altered in a specific and desired manner when compared to the wild-type protein.

Accordingly, Applicants submit that the computational method used to generate the integrin I domain proteins of the present invention is predictable and respectfully request that the rejection of Claims 1-7, 14, and 29-30 under U.S.C. §112, first paragraph be withdrawn.

b. Claims 1-7, 14, and 29-30 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed had possession of the claimed invention.

M.P.E.P. § 2163 states that possession of the claimed invention “may be shown in many ways.” These include a description of “an actual reduction to practice of the claimed invention. . . .” *Id.* An actual reduction to practice may be described “by showing that the inventor constructed an embodiment. . . that met all the limitations of the claim and determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 132, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998).” *Id.*

The Examiner has acknowledged that Applicants are in possession of three non-naturally occurring integrin I domain proteins stabilized in the open conformation (idolq, idolr, idol2r) and one non-naturally occurring integrin I domain protein stabilized in the closed conformation (jlm2r), and compositions thereof. The use of the disclosed proteins for their intended purpose is demonstrated by the results of

studies shown in Figures 2-4. Furthermore, each of the disclosed proteins is at least 98% identical to the wild-type protein. Applicants submit that these embodiments meet the claim limitations and, therefore, the written description requirement has been met.

The Examiner contends that Applicants' reduction to practice of the claimed invention is insufficient because "the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the" claimed genus. Applicants submit that this is not the proper standard when examining a patent application under the written description requirement. "The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement," which the Examiner cites, provides three alternative examples of fulfilling the written description requirement:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by [either] actual reduction to practice. . . , reduction to drawings. . . , or by disclosure of relevant identifying characteristics. . . .

Fed. Reg. 66(4):1099-1111, 1066 (2001) (emphasis added). Applicants submit that a representative number of species are disclosed by the actual reduction to practice of the non-naturally occurring integrin I domain proteins disclosed in the specification. Each of the disclosed proteins fulfill their respective claim limitations. Therefore, Applicants respectfully assert that specification meets the written description requirement of § 112, first paragraph.

In view of these remarks, Applicants respectfully request the rejection of Claims 1-7, 14, and 29-30 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Huang, *et al.* (1995) *Journal of Biological Chemistry* 270:19008-19016 (IDS Ref. No. C22). The Examiner contends that the disclosure by Huang, *et al.* of modified human LFA-1 proteins, which have three amino acid substitutions in noncontiguous regions in the integrin I domain and are 98.5% identical to the unmodified human sequence, anticipates the claimed invention. In making this rejection, the Examiner states that the term “about 98% identical” recited in Claims 1 and 2 reads on the 98.5% identity shared by the modified and wild type human LFA-1 proteins of Huang, *et al.*

Claim 1 is amended herein by the deletion of the term “about.”

Applicants respectfully assert that Claims 1 and 2 are novel in view of Huang, *et al.* and respectfully request the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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